REMARKS

Reconsideration of the above-identified application in view of the following remarks is respectfully requested.

Claims 1-23 are pending in this case. Claims 1-23 have been rejected. Claim 9 has now been canceled. Claims 1, 7 and 8 have now been amended.

35 U.S.C. § 102(e) rejection - Hanna

The Examiner states that claims 1-10 and 15-17 are rejected under 35 U.S.C. § 102(e) as being anticipated by Hanna (U.S. Patent No. 6,008,334). The Examiner's rejection is respectfully traversed. Claim 9 has now been canceled. Claims 1, 7 and 8 have now been amended.

Specifically, the Examiner states that Hanna discloses protected thiol analogs of pyrimidine bases for syntheses of DNA and RNA by chemical or enzymatic methods, whereby these nucleotide analogs can be incorporated into oligonucleotides and polynucleotides, deprotected and derivatized with a functional group. The Examiner further states that Hanna teaches that the thiol groups are preferably attached to the 5 position of the base and thus do not interfere with Watson-Crick pairing. The Examiner further states that the thiol groups in these analogs are attached to the ring by either a three, four, or five carbon chain.

The present invention is directed at modified nucleotides in which a purine or a pyrimidine base is substituted by a side chain **terminating** with a thiol group, which can be utilized to attach a metal (e.g., gold) cluster to the modified nucleotides. The side chain of the modified nucleotides of the present invention is selected long enough so as to eliminate the possibility of metal cluster-imposed stearic hindrance which can interfere with a base pairing ability of the modified nucleotide, with the use thereof in nucleic acid synthesis and/or with any other interaction of a nucleic acid to which it is incorporated.

Hanna teaches nucleotide analogs is which a pyrimidine base, namely, cytosine, uracil, or analogs thereof, is modified so as to have a protected thiol group attached thereto. As stated by the Examiner, Hanna teaches that the attachment of the

thiol group is performed at the 5 position of the base, which is not involved in or do not disrupt Watson-Crick base pairing.

Although Hanna teaches modified nucleotides which are designed capable of base pairing, such modified nucleotides are not designed while taking into consideration the effect of the thiolated group, particularly when attached to a functional group, on interactions of a nucleic acid sequence that includes such modified and functionalized nucleotides.

While the Examiner has stated that according to Hanna's teachings the thiol group is attached to the ring base by either a three, four, or five carbon chain, reviewing Hanna's patent uncovered that all the exemplary compounds set forth in the patent include a protected thiol group that is directly attached to the ring base. The Examiner's attention is directed in this respect to claims 1, 5, 12, 19 and 26, and to column 9, lines 57-67, in which preferred compounds according to Hanna are recited. These preferred compounds include, for example, 5-SDNP-U, 5-SDNP-C, 5-S-S-Et-U, 5-S-S-Et-C, and 5-S-CH_2NHCOCH_2Ph-C, whereby the thiol group in all of these compounds is directly attached to the pyrimidine base ring. The Examiner's attention is further directed to the paragraph bridging columns 10 and 11, to Example 1 and to Figure 1 in Hanna's patent, in which the most preferred compound according to Hanna, 5'-O-(4,4'-dimethoxytrityl)-5-S-(2,4-dinitrophenyl)mercapto-2'-deoxyuridine-3'-O-(2-cyanoethyl-N,N'-diisopropyl) phsophoramidite, its advantages and its synthesis are described.

As is clearly shown in Figure 1, the protected thiol group in this preferred compound is directly attached to the base ring. As is discussed, for example, in column 10, lines 55-57 and lines 62-65 of Hanna's patent, this compound is advantageous since it is easily and reproducibly synthesized, and can be stored for long periods. As is further discussed in Hanna's patent, this compound can be incorporated into a nucleic acid and can be radiolabeled and thus used to analyze DNA-protein interactions.

Hanna therefore disregards the effect of a relatively large moiety that is attached to a thiol-modified base, via the thiol group, on the functionality of the modified nucleotide in chain synthesis, stability and further interactions. Although the

Examiner states that Hanna describes side chains having 2-5 carbon atoms, Hanna does not address the fact that longer side chains might be necessary when attaching relatively large moieties such as metal clusters, largely because Hanna did not contemplate attachment of large metal clusters, but rather described attachment of relatively small molecules such as crosslinking agents and reporter molecules.

Contrary to Hanna, the present invention teaches modified nucleotides in which the thiol group is indirectly attached to the base ring via a side chain, whereby the side chain is selected long enough so as to enable the attachment of relatively large moieties such as metal clusters thereto, without affecting a nucleic acid chain synthesis, stability and other interactions.

Such modified nucleotides present numerous advantages over the modified nucleotides described by Hanna. By displacing the thiol moiety in a relatively large distance away from the base ring, the teachings of the present invention enable construction of modified nucleotides which can include thiol-attached functional moieties such as large metal clusters, since the use of a long side chain having at least 7 carbon atoms would eliminate any potential stearic hindrance forces exerted by such moieties.

The advantages of attaching functional groups to biomolecules via a relatively long side chain which will reduce the stearic interference of the functional group over such an attachment via a short or no side chain are widely taught in the art, (see, for example, "Methods in Enzymology", Bayer and Wilchek, eds., Vol. 184).

As is widely taught in the instant application, attachment of large moieties such as metal clusters to nucleic acids or oligonucleotides is highly advantageous, particularly with respect to applications which require visualization and elucidation of complexes formed between such nucleic acids and proteins. The present inventors have demonstrated the potential use of nucleic acid that are covalently labeled with metal clusters such as gold clusters for the structural characterization of protein-nucleic acid complexes, as well as in microelectronic devices (see, for example, Examples 5-7 of the instant application).

Since the present invention is directed toward modified nucleotides that are designed so as to enable labeling, via large moieties such as metal clusters,

oligonucleotides and polynucleotides, either *per se* or complexed with other biomolecules (e.g., proteins), which include such modified nucleotides, it is highly advantageous to have nucleotides in which the linking moiety, in this case the thiol moiety, is positioned in some distance from the base ring.

As is demonstrated in the Examples section of the instant application, preferred modified nucleotides according to the present invention were designed and synthesized such that the thiol group is attached to the ring base via a chain that includes at least 7 carbon atoms, and specifically, 8, 10 and 13 carbon atoms.

Thus, while Hanna teaches modified nucleotides to which a thiol group is directly attached to the base ring, the present invention teaches modified nucleotides in which the thiol group is indirectly attached to a base ring via a side chain that includes 7 or more carbon atoms. As is discussed hereinabove, such indirect attachment of a linking group such as thiol group to a nucleotide, which is only taught by the present invention, is highly advantageous particularly for diagnostic and analytical purposes. Since Hanna fails to teach or suggest modified nucleotides that enable attachment of large functional moieties (e.g., metal clusters) in such applications, thereto, it is clear that Hanna does not anticipate the nucleotide analogs of the present invention.

In order to more clearly distinguish the present invention from the teachings of Hanna, Applicant has chosen to amend independent claim 1, to include the limitation "... ***said side chain having at least 7 carbon atoms***".

Ample support for this limitation is found, for example, in the Examples section of the instant application (see, for example, Examples 1-4 and Schemes 3-5).

Applicant has further chosen to similarly amend dependent claims 7 and 8, to recite that the side chain has 7-20 carbon atoms and 7-15 carbon atoms, respectively. In view of these amendments, Applicant has further chosen to cancel claim 9, which recited a chain having 2-10 carbon atoms.

In view of these amendments, it is the Applicant's opinion that amended independent claim 1, claims 2-6, amended claims 7 and 8, claim 10 and claims 15-17, which directly or indirectly depend therefore are not anticipated by Hanna and are therefore allowable.

35 U.S.C. § 103(a) rejection – Hanna in view of Leone et al.

The Examiner states that claims 1-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanna (U.S. Patent No. 6,008,334, herein "Hanna's patent") in view of Leone et al. (U.S. Patent No. 6,369,206). The Examiner's rejection is respectfully traversed. Claim 9 has now been canceled. Claims 1, 7 and 8 have now been amended.

Specifically, the Examiner states that Hanna discloses protected thiol analogs of pyrimidine bases for syntheses of DNA and RNA by chemical or enzymatic methods, whereby these nucleotide analogs can be incorporated into oligonucleotides and polynucleotides, deprotected and derivatized with functional groups such as photocrosslinking agents, fluorescent tags, radioisotopes, biotin, reporter molecules, and spin labels, whereby Leone et al. disclose metal cluster compounds, particularly organothiol metal clusters, and a process for making such compounds. The Examiner continues stating that it would have been obvious at the time the invention was made to attach metal clusters as taught by Leone et al. to the analogs of Hanna, whereby the motivation would be to site-specifically attach functional groups by utilizing thiol-modifying agents.

Differences between the modified nucleotides of the present invention and those taught by Hanna are outlined above. While Leone et al. teach relatively large metal cluster organocompounds, attachment of such metal clusters to a base ring via a thiol group that is directly attached to the base ring, as taught by Hanna, would negatively affect any interactions formed between a nucleic acid sequence including such a modified base and other molecules (e.g., proteins) due to stearic hindrance forces exerted by the attached metal cluster.

It is therefore argued that since Hanna teaches modified nucleotides in which a thiol group is directly attached to the pyrimidine base ring, and since neither Hanna nor Leone et al. address the problems inherent to attachment of large metal clusters, the combined teachings of Hanna and Leone et al. fail to teach the present invention or motivate one of ordinary skill in the art to make the present invention.

Applicant therefore strongly believes that amended claim 1, as well as claims 2-6, amended claims 7 and 8 and claims 10-23, which directly or indirectly depend therefrom are patentable over Hanna in view of Leone et al. and are therefore allowable.

In view of the above amendments and remarks it is respectfully submitted that claims 1-8 and 10-23 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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